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Statins and venous thromboembolism: do they represent a viable therapeutic agent?

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Abstract

Introduction: Venous thromboembolism (VTE) is an important cause of preventable morbidity and mortality. Though anticoagulants are effective in preventing VTE, they are associated with major bleeding risk. The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (known as statins), are well established for the primary and secondary prevention of cardiovascular disease via their lipid-lowering properties. Emerging evidence suggests that statins may play a role in the prevention of VTE, but the evidence has been uncertain.

Areas covered: This review summarizes the available epidemiological and interventional evidence on the role of statins in VTE prevention; the postulated biologic mechanisms involved; outlines areas of outstanding uncertainty; and the implications for clinical practice.

Expert commentary: The body of evidence indicates statins may also play a potential role in the primary and secondary prevention of VTE. Further evidence is however warranted. There is insufficient evidence to recommend the use of statins to replace anticoagulants in VTE prevention. However, guideline bodies should review the overall evidence and consider including statin therapy as an adjunct to anticoagulant therapy in VTE prevention in specific patient populations. Statin therapy instead of anticoagulants may be considered in patients who are not candidates for anticoagulant therapy and in some low VTE risk patients.

KEYWORDS: Statins; venous thromboembolism; deep vein thrombosis; pulmonary embolism; prevention

1. Introduction

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE); DVT is the most frequent presentation of VTE, whiles PE is the most serious clinical presentation of VTE. Venous thromboembolism affects several millions of people worldwide. Globally, VTE has an annual incidence of 100-200 per 100,000 inhabitants and it is the third most common cardiovascular disease (CVD).[1, 2] In Europe alone, approximately 1.1 million VTE events occur each year and cause more than half a million deaths;[3, 4] whiles in the US, VTE events affect about 900,000 people annually, with up to 300,000 deaths.[3] Apart from being a preventable cause of deaths, VTE is an important cause of morbidity and associated with substantial healthcare costs.[4, 5] Though VTE is quite common in the elderly, major risk factors for VTE include major surgery such as lower limb total joint replacement, active cancer with or without concurrent chemotherapy, neurological disease with paresis of the lower limbs, prolonged bed stay as a result of hospitalization or nursing home confinement, trauma or fracture of lower limbs, oral contraception, and hormone replacement therapy (HRT).[4]

Primary and secondary prevention of VTE can be achieved by pharmacological and/or physical means. In primary prevention, pharmacological prophylaxis for VTE includes the use of low, fixed doses of anticoagulants such as unfractionated heparin, low-molecular weight heparin (LMWH), warfarin, or fondaparinux. For patients undergoing lower limb orthopaedic surgery (eg, total knee or hip replacement), novel oral anticoagulants (NOACs) (such as edoxaban, dabigatran, rivaroxaban, or apixaban) are available to use instead of heparin, warfarin, or fondaparinux.[6] Physical or mechanical measures such as graduated compression stockings, use of lower extremity compression devices, patient mobility, and rehabilitation are also considered in addition to these thromboprophylactic agents or are used for the at-risk patients who are not suitable candidates for pharmacological thromboprophylaxis. The American College of Chest Physicians (ACCP) and American Academy of Orthopedic Surgeons (AAOS) have recently recommended aspirin as an option for VTE prophylaxis in patients undergoing total joint replacement;[7, 8] however, the quality grading recommendation for its use as monotherapy is not high enough.[8] After an acute VTE event, anticoagulation is commenced for the purposes of preventing death and recurrent VTE events

(secondary prevention). With regards to secondary prevention, guideline bodies such as the ACCP and the European Society of Cardiology (ESC) recommend anticoagulation for a period of at least 3 months after a first VTE event.[9, 10] In the acute phase of a VTE event, parenteral anticoagulants such as unfractionated heparin, LMWH, or fondaparinux are the cornerstones of treatment and used over a period of 5-10 days. Parenteral heparin or fondaparinux needs to overlap with the commencement of a vitamin K antagonist (VKA) (warfarin, acenocoumarol, or phenindione) preferably started on the same day as the parenteral anticoagulant or alternatively can be followed by administration of one of the NOACs such as edoxaban or dabigatran.[10] Though the optimal duration of anticoagulant therapy after a first VTE episode is still subject to debate; it has been argued that a period of 3-6 months is adequate. In some specific patient populations, secondary prevention is extended beyond the initial period (3-6 months) and may continue indefinitely as long as the benefit-risk balance is favourable.[10] Anticoagulant therapy constitutes a double-edged sword; though it is effective in the primary and secondary of VTE, it is an inconvenient therapy and associated with high risk of bleeding.[11] Despite substantial progress made in understanding the epidemiology of VTE and the availability of effective primary and secondary prevention prophylaxis, there has been no decrease in its incidence for the past several decades.[12] Venous thromboembolism remains a global public health problem.[2]

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (commonly known as statins), are well established for the primary and secondary prevention of cardiovascular disease (CVD) and this is based on their lipid-lowering properties.[13, 14, 15] Statins reduce lipids by inhibiting cholesterol biosynthesis and promoting low-density lipoprotein (LDL) clearance from the circulation. Beyond their lipid-lowering properties, statins are also known to have several pleiotropic effects and these include improving endothelial function, decreasing oxidative stress and inflammation, enhancing stability of atherosclerotic plaques, decreasing platelet activation, inhibiting thrombosis, and inhibition of smooth muscle proliferation (**Figure 1**).[16] There have been suggestions that statins via their ability to modulate coagulation and inflammation,[17] might play a potential role in reducing the incidence of VTE. The role of statins in the prevention of VTE is of immense clinical interest and the past decade has witnessed the publication of several studies to clarify the role of statins in

preventing VTE. Till recently, the findings on the benefits of statins in VTE prevention have been mostly conflicting.

This review summarizes the available epidemiological and interventional evidence till date on the role of statins in the prevention of VTE; the postulated biologic mechanisms underlying these associations; outlines areas of outstanding uncertainty; and the possible implications for future clinical practice.

2. Statins and primary prevention of VTE

The effect of statins on primary prevention of VTE was initially brought to light through the publication of findings from the Heart and Estrogen/progestin Replacement Study (HERS) in 2002.[18] This study was a randomized clinical trial to evaluate the effects of estrogen and progesterone supplementation on cardiovascular events (morbidity and mortality) in 2,763 postmenopausal women with coronary heart disease (CHD). In a nonrandomized comparison of statin versus nonstatin users, an approximately 50 percent risk reduction in VTE was reported. In 2009, the first randomized controlled trial (RCT) - the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) - demonstrated that rosuvastatin significantly reduced the incidence of VTE.[19] This trial was based on 17,802 relatively healthy participants with high levels of high sensitivity C-reactive protein (hsCRP) and normal LDL-cholesterol levels. However, the few VTE events recorded suggested a statistical play of chance and this triggered calls for further studies to replicate these results.[20] Since the publication of these two landmark studies, several observational studies as well as RCTs have been published evaluating the role of statins in the primary prevention of VTE. Though a protective effect of statins on VTE risk has been suggested, the results of these studies have mostly been inconsistent. Given the inconsistency in the evidence, there were efforts to pool the evidence which resulted in a number of published reviews on the topic.[21, 22, 23] In an elegant meta-analysis of RCTs published in 2012, Rahimi and colleagues found no significant reduction in VTE events with statin therapy.[22] Given the publication of further trials after this study and the persisting uncertainty on the role of statins in the primary prevention of VTE, our group has recently published a comprehensive meta-analysis of 36 published studies (comprising

of 13 observational cohort designs and 23 RCTs) with data on more than 3.2 million participants.[24] In the observational studies, statin use was associated with a 25 percent reduced risk of VTE compared with no statin use. Similarly in RCTs, statin use reduced the risk of VTE compared with placebo by 15 percent (**Figure 2**). A subgroup analysis of our meta-analysis of RCTs showed that rosuvastatin was associated with the lowest risk of VTE (45 percent reduction) compared with other statins. Taking the all current evidence together, it can be suggested that statins may indeed have a true protective effect on VTE primary prevention.

3. Statins and secondary prevention of VTE

Patients with a first episode of VTE are at increased risk of recurrent episodes. The risk of VTE recurrence is said to vary with time after the first event; it is highest during the first 6-12 months, declines subsequently but never falls to zero.[25] Approximately 25 and 30 percent of patients with VTE experience a recurrence within 5 and 10 years respectively.[4, 26, 27] Although secondary prophylaxis is effective in the prevention of recurrence, patients with a first VTE are still at an elevated risk of a second episode. A recurrence rate of 3 percent has been reported during the first 3 to 6 months of anticoagulant therapy.[28, 29] It has been reported that beyond an initial 3 months of prophylactic anticoagulation, the duration of acute therapy does not influence the rate of VTE occurrence.[4] Some patients with a first VTE such as those whose VTE is cancer-related or those with an unprovoked or idiopathic PE, usually require an extended duration of anticoagulation because their overall risk of recurrent VTE is substantially increased.[30, 31] Apart from the need for frequent laboratory monitoring and dose-adjustments which is associated with long-term anticoagulation, there is an increased risk of major bleeding; reducing the risk of VTE recurrence with anticoagulant therapy has been associated with about a 5-fold increase of major bleeding.[32] Venous thromboembolism recurrence is a major clinical problem and of public health importance. Compared to primary prevention, the role of statin therapy in the secondary prevention of VTE is limited. Randomized controlled trials on the role of statin therapy in VTE recurrence are not available to make concrete conclusions about the value of statins in the secondary prevention of VTE. However, a number of observational studies have been conducted, but their results have been inconsistent.[33, 34] In a recent

pooled analysis of 8 available studies comprising of 103,576 participants and 13,168 recurrent VTE events,[35] our group has shown that statin use is associated with a reduced risk of recurrent VTE as well as DVT and PE (**Figure 3**). Secondary prevention of VTE may be another potential indication of statins; however, well-designed intervention studies are now needed to corroborate this evidence.

4. Postulated mechanisms

Several factors are implicated in the etiopathogenesis of VTE and these include alterations in blood flow and the coagulation cascade, endothelial dysfunction, and hypercoagulable states.[36] It has also been postulated that an inflammatory hypothesis may be involved, but the evidence is unclear and remains a subject of considerable debate.[37, 38] Inflammatory markers such as CRP are well known to be associated with an increased risk of atherothrombosis[39, 40] and may also promote hypercoagulable states, but whether inflammation actually increases the risk of VTE is not very certain.

Various mechanisms have been proposed to explain the protective effect of statins on the risk of VTE and these include (i) statins downregulate the blood coagulation cascade, leading to reduced tissue factor (TF) expression and which causes reduced thrombin formation;[41, 42, 43, 44] (ii) statins cause increased expression of thrombomodulin on the endothelial cells, which may enhance the activity of the protein C anticoagulation system, thereby inhibiting the coagulation cascade;[45] (iii) statins may decrease the susceptibility for thrombosis and coagulation, by decreasing plasminogen activator inhibitor-1 expression[46] and increasing tissue plasminogen activator; (iv) statins decrease the coagulant activities of factors VII and VIII and reduce factor XIII activation; [47] (v) statins have also been suggested to reduce the risk of VTE via reduction in plasma levels of D-dimer, enhanced fibrinolysis and inhibitory effects on platelet aggregation;[48, 49, 50] and (vi) statins may reduce the risk of VTE by modulating fibrin clot properties, which has been demonstrated in both healthy individuals and those with previous VTE;[51] indeed, a recent review has suggested that abnormalities in fibrin clot properties may contribute to the pathogenesis of VTE.[52] Statins may also reduce the risk of VTE by modulating the activity of FVIII.[53] It has been reported that the decrease in FVIII activity as a result of statin use, usually occurs in association with decreased levels

of von Willebrand factor.[54] Furthermore, the beneficial effects of statins on VTE have also been attributed to its anti-inflammatory effects.[55] Indeed, several inflammatory markers such as CRP, the interleukins, and tumour necrosis factor alpha have been shown to be associated with an increased risk of VTE.[56, 57, 58] Findings from the JUPITER trial demonstrated that 20 mg/day of rosuvastatin therapy in healthy men and women lowered hsCRP levels by 37 percent and resulted in an approximately 50 percent relative reduction in VTE risk.[19] Taking these results and the positive association between CRP and VTE risk, it has been suggested that some of the reduction in VTE risk by statins may occur as a result of reduction in inflammation.[59] Finally, though the VTE preventive effect of statins appears to be independent of their cholesterol lowering effects; whether this is really the case has been the subject of considerable debate.[60] Apart from the fact that arterial atherothrombosis and VTE are closely linked [61, 62, 63] and share common antecedent risk factors,[64] they also share common therapies for prevention and/or treatment which include aspirin, heparin, and warfarin.[60] Dyslipidemia, an established risk factor for arterial thrombosis, has also been implicated in the development of VTE.[60] Indeed, hypercholesterolemia has been shown to produce a procoagulant state[65] and is associated with platelet hyperactivity;[65, 66] which goes to suggest that statins may reduce the risk of VTE via lowering of lipid levels. However, emerging evidence suggests this is not the case. In the JUPITER trial, there was a substantial reduction in risk of VTE on administration of rosuvastatin to subjects with normal LDL but elevated levels of hsCRP.[19] The authors speculated that the reduction in thrombosis might be due to the inhibition of TF expression by statins, but this could not be proved in the trial. In a recent experimental study, Owens et al.[67] demonstrated that hypercholesterolemia causes a prothrombotic state via elevation in levels of oxidized LDL (oxLDL) in plasma which induces TF expression. The investigators also showed that simvastatin inhibited oxLDL induction of TF expression in animal and human cells and concluded that the ability of statins to reduce VTE in hypercholesterolemic patients might be via their ability to reduce TF expression. These multiple biological effects could potentially explain the protective effects of statins on the incidence of VTE; however, further study is still warranted.

5. Conclusions

Taking previous and the recent body of evidence together suggests that statins may have a potential role to play in both the primary and secondary prevention of VTE in addition to their established role in CVD prevention. Indeed, the extensive body of evidence may support a true protective effect on VTE. The question is should statins be prescribed solely to reduce the risk of VTE based on the current evidence? The answer is an emphatic no. Prevention of VTE may be another potential indication of statins; however, it is still too early to expand guidelines for statins use to include prevention of VTE. It should be borne in mind that there were some limitations to the two recent reviews on the role of statins in the primary and secondary prevention of VTE.[24, 35] In the meta-analysis of primary prevention of VTE,[24] the majority of trials included in the pooled analysis did not specify VTE as a primary endpoint, but recorded the incidence of VTE as adverse events. In the review of secondary prevention of VTE,[35] pooled analysis was based on a limited number of studies which were observational cohort designs. Interventional evidence is therefore needed to corroborate this finding. Indeed, further robust evidence is warranted to establish any potential true protective effect of statins on VTE. Furthermore, whether statins reduce the risk of VTE in high risk populations, such as patients who have had a lower limb total joint replacement, is uncertain at the moment; as the majority of primary prevention previous studies conducted on the topic have been mainly based in patients at low VTE risk and those with pre-existing CVD.[24] According to unpublished research presented at the 2014 Annual Meeting of the AAOS, in a retrospective cohort of patients who had undergone elective total knee and hip replacements, statins in addition to conventional VTE prophylactic therapy significantly reduced the risk for post-operative VTE events by 48 percent when compared with the non-statin group.[68] The authors also estimated that 14 joint replacement patients will need to be treated with statins to avoid one VTE event. Though statins may not be solely prescribed to reduce the risk of VTE based on the current evidence, guideline bodies should consider including statin therapy as an adjunct to anticoagulant therapy in VTE prevention in some specific patient populations. Despite anticoagulants being very effective for reducing the risk of VTE, they are commonly associated with increased risk of major haemorrhage which can be fatal. In

addition, high rates of VTE have still been reported in people who have received anticoagulant therapy. Since most patients who experience VTE generally tend to have prevalent medical conditions such as CHD and dyslipidaemia, the use of statins may be beneficial in the prevention of VTE and these comorbidities in combination. However, not everybody will agree to this recommendation for various reasons.

Though statins have been in use for several decades and the amount of evidence showing the beneficial effects of taking statins in cardiovascular prevention is substantial, there is still a lot of debate as to whether statins should be prescribed to everybody at high cardiovascular risk or not. It has been argued by some health professionals that the risks of statins outweigh the benefits for patients with lower cardiovascular risk. Cost implications have also been reported. Though side effects are generally associated with the use of statins, majority of these have been generated as a result of media hype. Statins are generally safe and well tolerated and published evidence suggests that only a small fraction of side effects reported by people are attributable to common doses of statins.[69] The most common and important adverse side effects of statins include muscle pain, an increased risk of diabetes, and increased blood levels of liver enzymes.[70, 71, 72] Whiles the majority of people taking statins won't experience these side effects, muscle-related symptoms generally resolve rapidly once treatment is stopped.[72] The majority of people who develop early onset diabetes as a result of statin therapy are those people who are already at high risk. Moreover, most people with diabetes are also prescribed statins because of their high risk of developing CVD. Finally, statins are very cheap drugs as the majority are now off patent and compared with anticoagulants, statins do not cause an increased risk of bleeding.

6. Expert commentary

The broad body of evidence indicates that statins may play a potential role in the primary and secondary prevention of VTE in addition to their established role in CVD prevention. Further robust evidence however is needed to establish these roles. The evidence is much stronger for primary prevention, as a number of RCTs have been able to demonstrate a beneficial role of statins in VTE risk reduction. However, the findings from these trials could be biased as they were mostly based on

VTE collected as safety or adverse events. For secondary prevention, the evidence is limited and has been mostly based on analysis of administrative data. Further robust evidence in the form of well-designed large-scaled trials are needed to establish these potential additional roles of statins. Intervention studies in very high-risk populations are also warranted. It has however been debated that such trials are unlikely to be feasible in the near future, since the number of patients needed to be recruited are prohibitively large.[73] There may be a challenge in conducting such trials, but this is not impossible. The Heart Protection Study of cholesterol lowering with simvastatin recruited over 20,000 high-risk individuals,[14] though it failed to demonstrate any protective effect of statins on VTE risk despite the relatively substantial number of VTE events recorded. It is uncertain why there was a lack of a protective effect, but this could be attributed to the type of statin used. Whether the effect of statins on VTE is a class effect is not clear, but recent evidence from a review showed that rosuvastatin (a newer type of statin) reduced the risk of VTE compared with other statins;[24] though a head-to-head comparison was not possible due to the limited data. Indeed, a number of studies have suggested that rosuvastatin is more effective at lowering LDL-cholesterol compared with other statins.[74, 75, 76] Future trials should also evaluate if the protective effect of statins is a class effect. There is currently insufficient high quality evidence for guideline bodies to recommend the use of statins to replace anticoagulants in reducing the risk of VTE, especially in high-risk patients who require thromboprophylaxis with anticoagulants. However, in the absence of robust clinical trial evidence, relevant guideline bodies should review the overall body of evidence and consider including statin therapy as an adjunct to anticoagulant therapy in VTE prevention in some specific patient populations. Patient populations that may benefit from statin therapy as primary or secondary prophylaxis in addition to anticoagulant therapy are those at very high risk of a first or recurrent VTE, such as patients who have undergone major surgery such as lower limb total joint replacement, patients with active cancer with or without chemotherapy, patients with neurological disease with paresis of the lower limbs, as well as patients with a first unprovoked PE. Statins may be effective adjuncts to anticoagulant therapy in such patients as high VTE rates including fatal PE events are still reported in patients who have received anticoagulant therapy. As regards to the best time to commence treatment, statin therapy should always be initiated early as these drugs take a few weeks

to exhibit their effects. For example in patients who are about to have a low limb total joint replacement, statin therapy could be started 1-2 weeks before the surgery. Different statins vary in their potency and their onset of action, and therefore these factors need to be taken into account when initiating therapy.

Statins may be considered in place of anticoagulants in some patient populations who are not suitable candidates for anticoagulant therapy and patients who are at low risk of VTE to minimize the risk of bleeding associated with anticoagulant therapy; but this decision should be taken on an individual patient basis by the attending healthcare professional after careful evaluation of the risk profile of the patient and a trade-off between benefits and risks, particularly the risk of a VTE. In addition, other prophylactic measures such as enhancing mobility and the use of graduated compression stockings or lower extremity compression devices should be instituted in such patients. Instances where statins could be used instead of anticoagulants include (i) long-term primary prevention of VTE among patients undergoing ambulatory anti-cancer chemotherapy, who are at moderate risk of VTE and generally do not require anticoagulant prophylaxis, but have an elevated risk of major bleeding with anticoagulant therapy;[77, 78] (ii) the secondary prevention of VTE following the completion of an initial course of anticoagulant therapy after an idiopathic VTE event; in this patient group, the risk of recurrence is at the highest in the first 3 months and subsequently declines after this period;[60] (iii) patients with a first VTE provoked by transient or reversible factors such as immobilization, surgery, trauma, or HRT, as these patient populations have a lower risk of VTE recurrence;[31] and (iv) patients who are at low VTE risk and have comorbidities such as CHD and dyslipidaemia. To re-iterate the point again, consideration of the use of statins without the need for anticoagulants should be decided on an individual basis after careful evaluation of the risk-benefit ratio.

7. Five-year view

The potential role of statins in the prevention of VTE is a subject of much debate and has important implications for clinical practice. In primary prevention, pooled evidence from several observational cohorts as well as interventional studies show that statins reduce the risk of VTE. In secondary

prevention, pooled limited observational evidence also suggests that statins may reduce VTE recurrence. However, based on the limitations of previous studies, there isn't enough robust evidence to inform major guideline recommendations.

In 5 years, it is expected that more robust large-scale studies will have further elucidated the beneficial role of statins in VTE prevention, especially for secondary prevention where the evidence is quite limited. Further studies clarifying the mechanistic pathways by which statins reduce the risk of VTE is also expected.

8. Key issues

- Observational and interventional studies indicate that statins may play a potential role in the primary prevention of VTE.
- A class effect of statins in the primary prevention of VTE is unclear because of limited evidence. However, existing evidence indicates that rosuvastatin substantially reduces VTE risk compared with other statins.
- Limited observational data suggests that statins may play a potential role in the secondary prevention of VTE.
- Well-designed large-scale trials are needed to confirm the role of statins in the primary and secondary prevention of VTE.
- Intervention studies are also needed in at high-risk VTE populations such as patients undergoing lower limb total joint replacement.
- Statins should not replace anticoagulants to reduce the risk of VTE. However, in the absence of robust evidence, guideline bodies should review the evidence and consider including statin therapy as an adjunct to anticoagulant therapy in VTE prevention in some specific patient populations, such as those at very high risk of VTE.
- Statin therapy instead of anticoagulants may be considered in patients who are not suitable candidates for anticoagulant therapy and in some populations who are at low VTE risk, to minimize the high bleeding risk associated with anticoagulant therapy. However, this needs to be

decided on an individual patient basis after careful evaluation of the risk profile of such patients and weighing the benefits against the risks.

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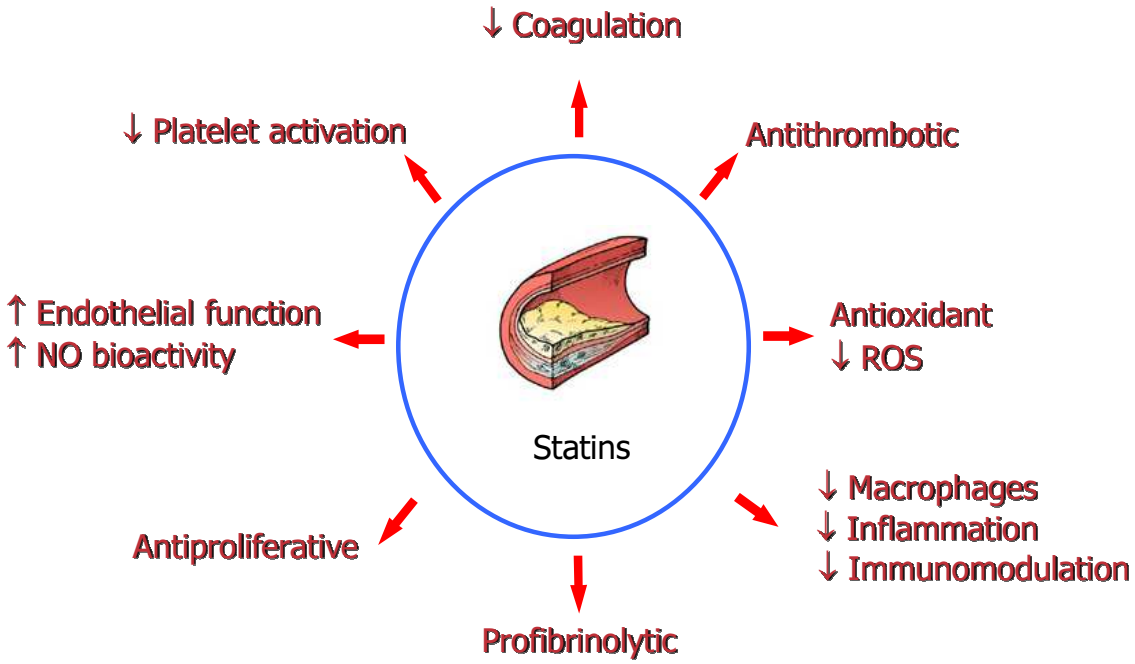
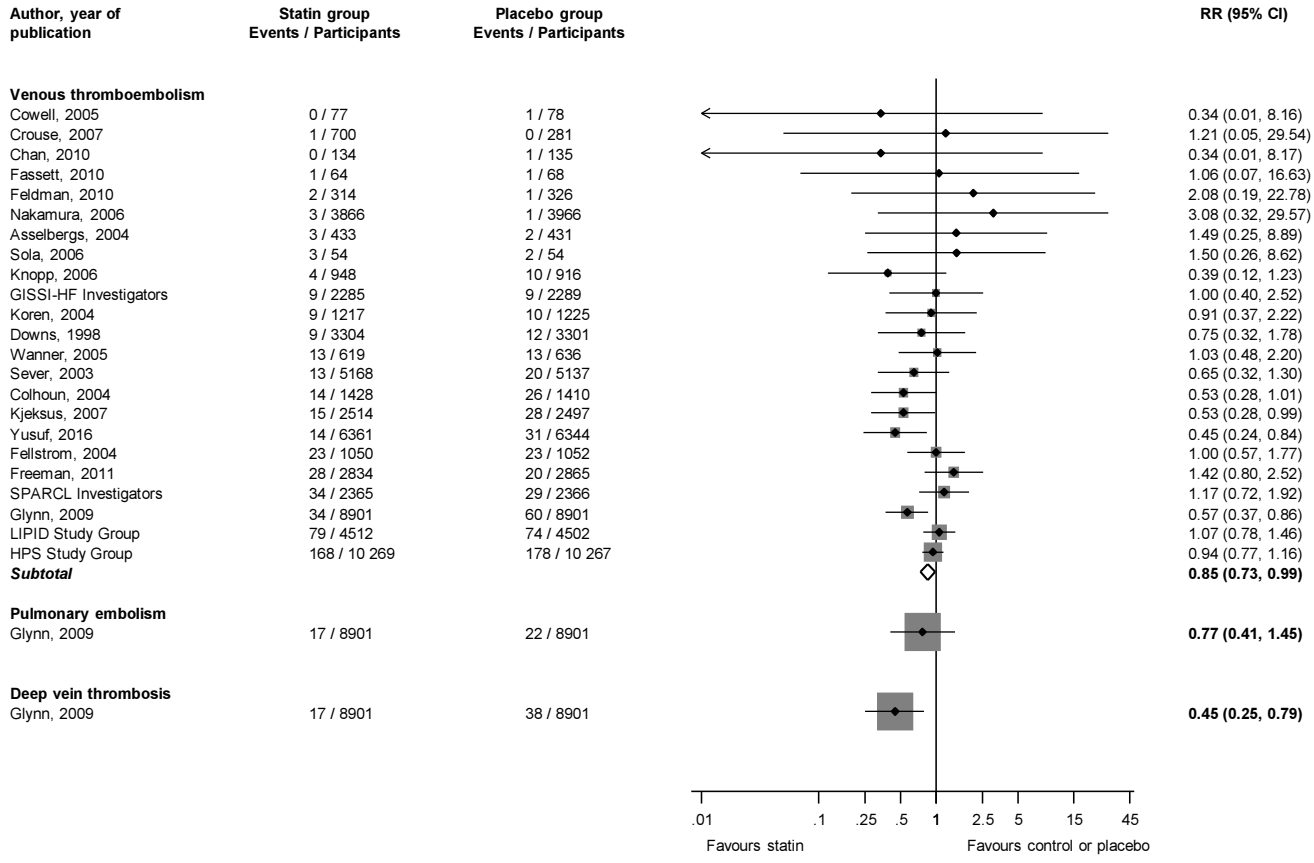
Figure Legends

Figure 1: Pleiotropic effects of statins



NO, nitric oxide; ROS, reactive oxygen species

Figure 2: Effect of statin therapy on primary prevention of venous thromboembolism in pooled analysis of randomized controlled trials



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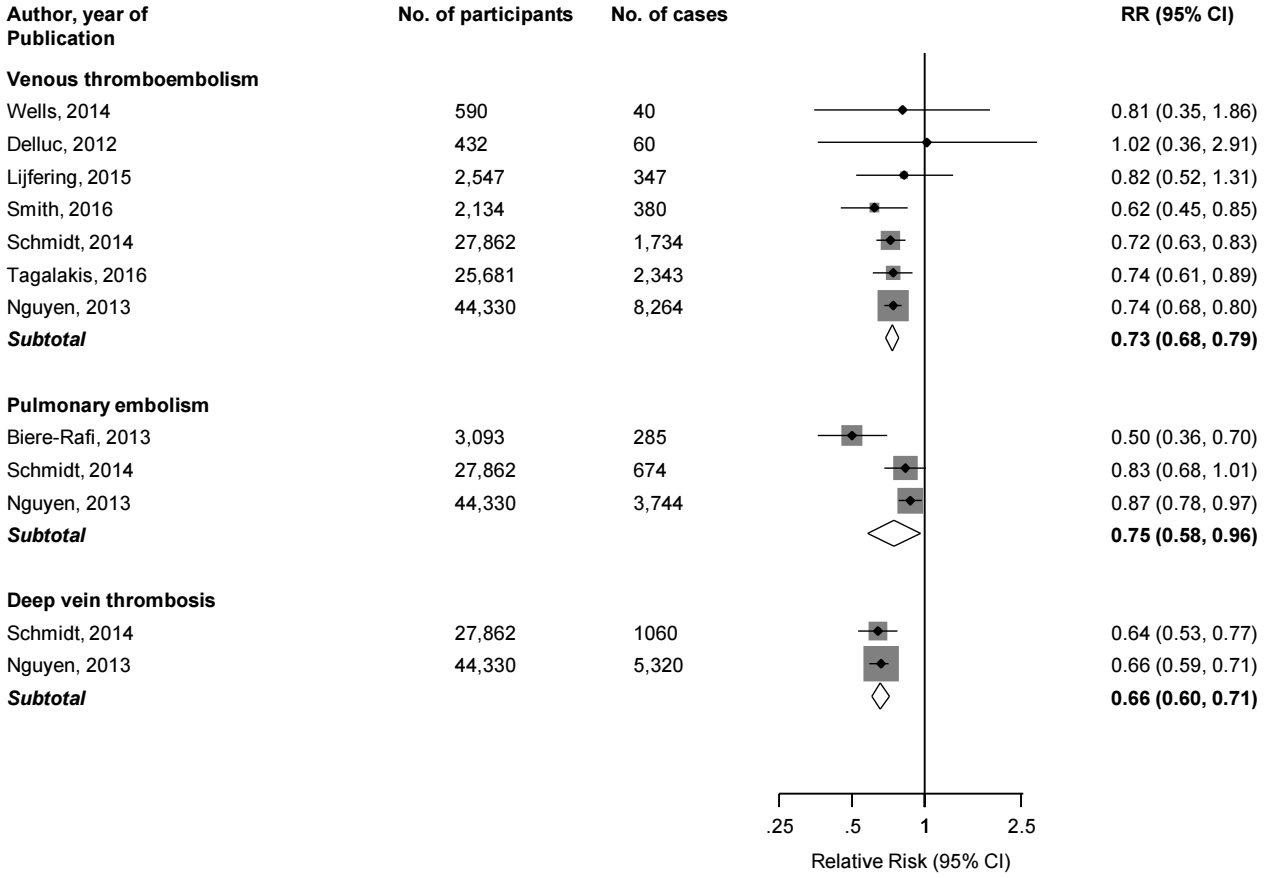
CI, confidence interval; RR, relative risk

Figure 3: Association of statin use with risk of recurrent venous thromboembolism in pooled analysis of observational cohort studies



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CI, confidence interval; RR, relative risk